

II. Rejections under 35 U.S.C. §103

Claims 24, 26-27 and 35 were rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 5,708,153 (Dower *et al.*). The rejections are respectfully traversed in light of the following remarks.

A. The Invention

A1. The Claims

The applicants' invention, as embodied in independent claim 24, is directed to an array of polynucleotides, the array comprising:

a closely packed planar array of microparticles, where the array has either (1) a number of microparticles per unit area in the planar array that is at least eighty percent of the number of microparticles in a hexagonal array of equal area or (2) an average distance between centers of adjacent microparticles that is less than two microparticle diameters; and

a plurality of different polynucleotides attached to the microparticles, such that each different polynucleotide is attached to a different microparticle. Stated differently, this means that no single microparticle contains more than one kind of polynucleotide.

A2. Benefits of the Invention

The invention allows large numbers of polynucleotide-containing microparticles, which are useful for, e.g., synthesizing, sorting, sequencing, screening, or otherwise manipulating large numbers of such polynucleotides, to be tracked through multiple steps of a process for analytical purposes. (See, for example, the Background of the Invention, pages 1, line 23 to page 2, line 3 of the specification.) The closely packed array allows individual microparticles to be repeatedly observed and tracked through a series of processing steps, and allows a large number of microparticles to be processed in a workable area. See, for example, page 23, lines 1-2: "Three cycles of ligation, identification, and cleavage are carried out in flow chamber (201) to give the sequences of 12 nucleotides at the termini of each of approximately 500,000 cDNAs" (on as many microparticles). The subsequent steps on this page describe repeated cycles of imaging and chemical processing (in this case, for sequencing) of the polynucleotides on the beads. Because the polynucleotides are on array of microparticles, rather than a fixed array, the polynucleotides can also be subjected to operations such as sorting, which would not be possible with a fixed array.

B. The Cited Art

Dower (U.S. Patent No. 5,708,153, entitled "Method of Synthesizing Diverse Collections of Tagged Compounds") is directed to a method of synthesizing diverse collections of tagged molecules on a plurality of solid supports such as beads. The process is described as follows (column 7, lines 28-41; emphasis added):

"The oligomer sequence is synthesized in a process comprising the steps of:

- a) **apportioning the supports** in a stochastic manner among a **plurality** of reaction vessels;
- b) exposing the supports in each reaction vessel to a first monomer;
- c) **pooling** the supports;
- d) **apportioning the supports** in a stochastic manner among the **plurality** of reaction vessels;
- e) exposing the supports in each reaction vessel to a second monomer; and
- f) repeating steps a) through e) from at least one to twenty times."

C. Analysis

1. Standard of Obviousness

In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references or in knowledge generally available to one skilled in the art, to modify a reference or combine reference teachings. The prior art must also provide a reasonable expectation of success. Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. (MPEP §2143)

This standard has not been met. The Dower reference does not show or suggest critical elements of the claims, and does not provide any reasonable motivation to modify its teachings along the lines of the invention. In particular, the reference does not show or suggest a "closely packed planar array" of microparticles.

The synthesis process of Dower, described above, follows the "mix and split" methodology of producing libraries of compounds. The aspect of pooling (mixing) the supports and then reapportioning them at each step is crucial to the production of the diverse library of compounds. (See, for example, column 9, lines 43-48 of the reference: "...This shuffling process produces solid supports with many oligomer sequence combinations.") Accordingly, the reference provides no motivation to provide the supports in a "closely packed planar array". Since the supports are to be repeatedly pooled, apportioned, repooled, and reapportioned, any effort spent in arranging the supports in a "closely packed planar array", as claimed, would be entirely wasted.

The libraries can also be used for screening, as described at column 17, lines 13-55. For

example, the beads can be exposed to a surface bearing a receptor, after which the unbound beads are washed away, and bound beads are eluted and separated (column 17, lines 40-47). Again, there would be no reason to arrange the beads in "closely packed planar array", as claimed, for such a process.

2. The Examiner's Arguments

In the Office Actions, the Examiner has placed great emphasis on the assertion that "Dower *et al.* do disclose the synthesis of peptides on 96 plastic pins which fit the format of standard microtiter plates", and that this somehow suggests the planar array of microparticle-bound polynucleotides claimed by the applicants. This reasoning is misplaced for the following reasons:

a) Dower's "disclosure" of synthesis on 96 plastic pins occurs only in the Background of the reference, where Dower describes the deficiencies of such a method in producing libraries of compounds (column 2, lines 35-40). The teachings of Dower are directed to a "mix-and-split" synthesis strategy, as described above, and the advantages of such a strategy (i.e., the ability to create diverse libraries by mixing and reapportioning the supports) over the "synthesis of peptides on 96 plastic pins".

Therefore, Dower actually teaches away from the use of such an array of pins. The reference in no way suggests that the use of microparticles should be combined with the use of such an array (as the Examiner seems to imply). As noted above, arranging "mix and split" synthesis particles into an array would be a complete waste of effort.

b) Even if the Dower reference were directed to synthesis on 96 pins, such an array of pins would in no way suggest the array of microparticles presently claimed, or the advantages thereof. The use of microparticles as claimed allows large numbers (as many as 500,000 or more) of attached polynucleotides to be sorted, sequenced, or otherwise manipulated, followed by placement in the closely packed planar array for tracking through multiple steps of a process, typically for analytical purposes. These advantages could not be provided by a fixed array of any number of pins.

The discussion above establishes that the Dower reference does not show or suggest critical elements of the claims, and does not provide any reasonable motivation to modify its teachings along the lines of the invention. Accordingly, the applicants respectfully request that the rejections over Dower be withdrawn.

III. Further Rejections under 35 U.S.C. §103

Claims 24 and 28 were rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 5,708,153, above (Dower *et al.*), in view of U.S. Patent No. 5,429,807 (Matson *et al.*). The rejections are respectfully traversed in light of the following remarks.

A. The Invention

The invention of independent claim 24 is described above. Dependent claim 28 is directed to an embodiment in which the planar array of microparticles of claim 24 is disposed in a flow chamber.

B. The Cited Art

Dower et al., as described above, is directed to a method of synthesizing diverse collections of tagged molecules on solid supports, in which the supports are repeatedly apportioned, pooled, and reapportioned between synthetic steps.

Matson et al. describes an applicator plate device having a plurality of synthesis reagent channels, used for preparing a corresponding plurality of different-sequence biopolymers on a second plate surface (e.g., column 1, lines 44-47 and 61-62; column 2, lines 8-10; column 3, lines 45-46; column 5, lines 62-64; see also Fig. 6). By rotating the channel-containing ("applicator") plate with respect to the second plate, another, overlapping, plurality of sequences can be formed on the second plate, with multiple sequences at each overlapping position (e.g. column 1, line 67 to column 2, line 11; sentence bridging columns 6-7).

C. Analysis

1. Standard of Obviousness

In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references or in knowledge generally available to one skilled in the art, to modify a reference or combine reference teachings. The prior art must also provide a reasonable expectation of success. Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. (MPEP §2143)

This standard has not been met. The discussion below establishes that the Dower and Matson references, alone or in combination, do not fairly suggest critical elements of the claims, and provide no reasonable motivation to combine their teachings, or to modify their teachings along the lines of the invention.

- a) Neither reference shows or suggests a "closely packed planar array of microparticles".

This has been established above for the Dower reference.

The Matson reference, as described above, teaches a single support having a large plurality of different sequences, even at single positions on the support, which is directly contrary to the language of the present claims ("a closely packed planar array of microparticles" in which "each different polynucleotide is attached to a different microparticle").

b) The cited art provides no motivation to modify the Matson reference along the line of the invention.

The plurality of sequences affixed to the plate in Matson are used for hybridization analysis (see e.g. the Field of the Invention). The cited references provide no motivation to prepare such a plurality of sequences, for use in hybridization analysis, on an array of microparticles, as claimed, rather than on a single planar support, as shown in Matson.

Furthermore, because the synthesis channels in Matson are used simply for transfer of synthetic reagents onto corresponding regions of a second plate (see e.g. Fig. 6), there would be no motivation to fill these channels with a "closely packed planar array of microparticles", as claimed, or with any microparticles.

Nor would an array of sequences affixed to a single solid support, as taught by Matson, be appropriate for sorting, sequencing, or other manipulation, followed by tracking through a series of analytical steps in a closely packed array, as described in the applicants' specification. The systems are not interchangeable, in spite of the Examiner's rather facile assertion that "there is no big difference between using microparticle[s] and glass slide to synthesize DNA".

c) There is no motivation to combine the teachings of the references.

The references provide no motivation to combine the teachings of Dower with those of Matson. The Examiner suggests that one would be motivated to place the beads used by Dower into one of the reagent channels disclosed in Matson. However, this would serve no purpose in the Matson device, and would actually defeat the purpose of Dower, since the channel would be totally inappropriate for the pooling and reapportioning of beads as described in Dower. "A modification which defeats the purpose of a primary reference, or renders it inoperative, cannot be considered obvious." *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984).

2. The Examiner's Arguments

Case law has established that the Examiner may not "pick and choose among the individual elements of assorted prior art references to recreate the claimed invention," but rather, must look for

"some teaching or suggestion in the references to support their use in the particular claimed combination." *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569, 19 USPQ2d 1241 (Fed. Cir. 1991). Further to this point, "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." *Bausch & Lomb v. Barnes-Hind/Hydrocurve* (796 F.2d 443, 230 USPQ 416, Fed. Cir. 1986)

In the Office Actions, the Examiner has attempted to combine disparate elements disclosed in the separate references (and sometimes even disparaged in the references), e.g. a collection of microparticles, an attached oligonucleotide, a fixed array of pins, a fixed array of molecules on a plate; to recreate the subject matter of the claims. However, the Examiner has clearly failed to show that the references provide any motivation to combine their teachings along the line of the invention, or even that such a combination could produce the claimed invention.

In view of the above, the applicants respectfully request that the rejections over Dower and Matson be withdrawn.

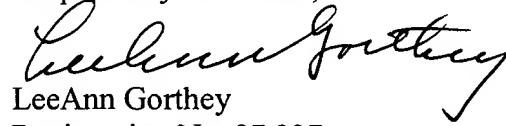
IV. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

No further fees are believed necessary with this communication. However, the Commissioner is hereby authorized and requested to charge any deficiency in fees herein, or credit any overpayment, to Deposit Account No. 50-0665.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4403.

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